EARLY DECREASE OF TYPE 1 CANNABINOID RECEPTOR BINDING AND PHOSPHODIESTERASE 10A ACTIVITY IN VIVO IN R6/2 HUNTINGTON MICE

Maarten Ooms [1,2], Roma Rietjens [2,3], Janaki Raman Rangarajan [4], Kathleen Vunckx [3], Sara Valdeolivas [5], Frederik Maes [4], Uwe Himmelreich [2,6], Javier Fernandez-Ruiz [5], Guy Bormans [1,2], Koen van Laere [2,3], Cindy Casteels[2,3]

[1]KU Leuven Laboratory of Radiopharmacy, Herestraat 49, 3000 Leuven, Belgium

[2]KU Leuven Molecular Small Animal Imaging Centre (MoSAIC), Herestraat 49, 3000 Leuven, Belgium

[3]KU Leuven and University Hospital Leuven Division of Nuclear Medicine and Molecular Imaging, Herestraat 49 bus 505, 3000 Leuven, Belgium

[4]KU Leuven Medical Image Computing (ESAT/PSI) Department of Electrical Engineering & Medical Imaging Research Center, Herestraat 49, 3000 Leuven, Belgium

[5]Universidad Complutense de Madrid Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Madrid,Spain

[6]KU Leuven Biomedical NMR Unit, Herestraat 49, 3000 Leuven, Belgium

Introduction

Several lines of evidence imply early alterations in endocannabinoid and phosphodiesterase 10A (PDE10A) signaling in Huntington's disease (HD). Using [^{18}F]MK-9470 and [1^{8}F]JNJ42259152 small-animal PET, we investigated for the first time cerebral changes in type 1 cannabinoid (CB1) receptor binding and PDE10A levels in vivo in pre-, early- and late symptomatic HD (R6/2) mice, in relation to brain morphology (MRI) and motor function.

Methods

Ten R6/2 and 16 wild-type (WT) mice were investigated at 3 different time points between the age of 4 and 13 weeks. Parametric CB1 receptor and PDE10A images were anatomically standardized to Paxinos space and analyzed voxel-wise. Volumetric microMRI imaging was performed to assess HD pathology.

Results

In R6/2 mice, CB1 receptor binding was decreased in comparison to WT in the bilateral caudateputamen, globus pallidus and thalamic nucleus at week 5 (-8.1%, p_{height} =1.7.10^{-5}). Longitudinal follow-up showed further progressive decline compared to controls in a cluster comprising the bilateral hippocampus, caudate-putamen, globus pallidus, superior colliculus, thalamic nucleus and cerebellum (late vs. presymptomatic age: -13.7±3.1% for R6/2 and +1.5±4.0% for WT; p_{height} =1.9.10^{-5}; Fig. 1). In R6/2 mice, PDE10A binding potential also decreased over time, to reach significance at early and late symptomatic HD (late vs. presymptomatic age: -79.1±1.9% for R6/2 and +2.1±2.7% for WT; p_{height} =1.5.10^{-4}; Fig. 2). The observed changes in CB1 receptor and PDE10A binding were correlated to anomalies exhibited by R6/2 animals in motor function, while no correlation was found with MRI-based striatal volume.

Conclusions

Our findings point to early regional dysfunctions in endocannabinoid and PDE10A signaling, involving the caudate-putamen and lateral globus pallidus, that may play a detrimental role in the progression of the disease in R6/2 animals. PET quantification of in vivo CB1 and/or PDE10A binding may thus be useful early biomarkers for HD. Our results also provide evidence of subtle motor deficits at earlier stages than previously described.

Acknowledgement / References

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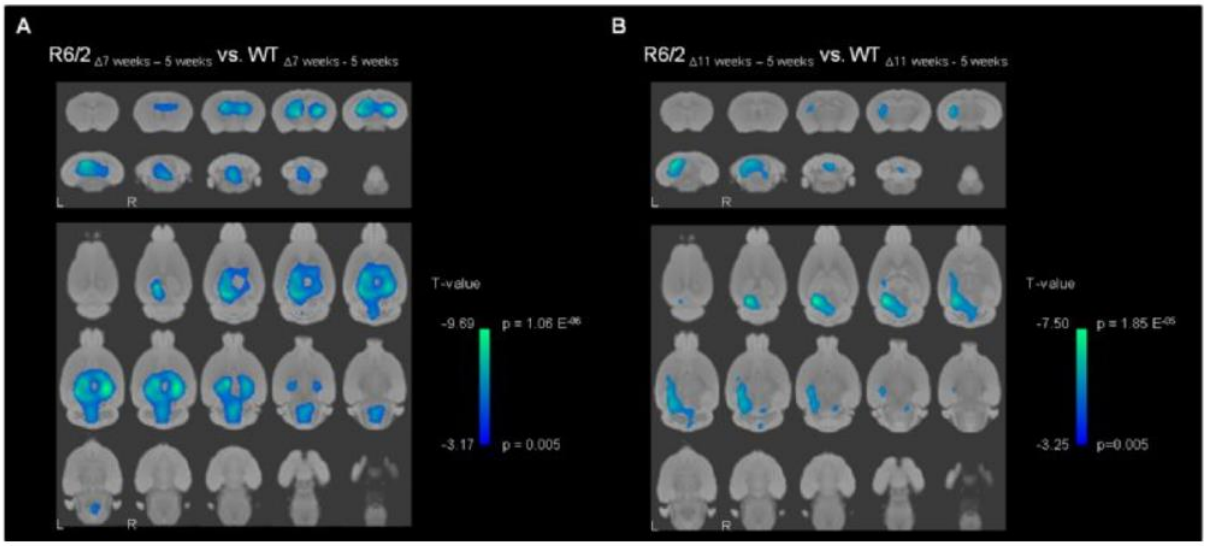

Fig1:CB1 Receptor in R6/2: (A-B) Coronal and axial brain sections showing decreased [18F]MK-9470 binding in R6/2 mice over time, as compared to WT littermates. Significance is shown with a T statistic color scale. Images are in neurological convention.

Image 1 of 2

Consortium (KUL PF/10/017). Cindy Casteels is supported by a post-doctoral mandate of the Research Foundation Flanders.

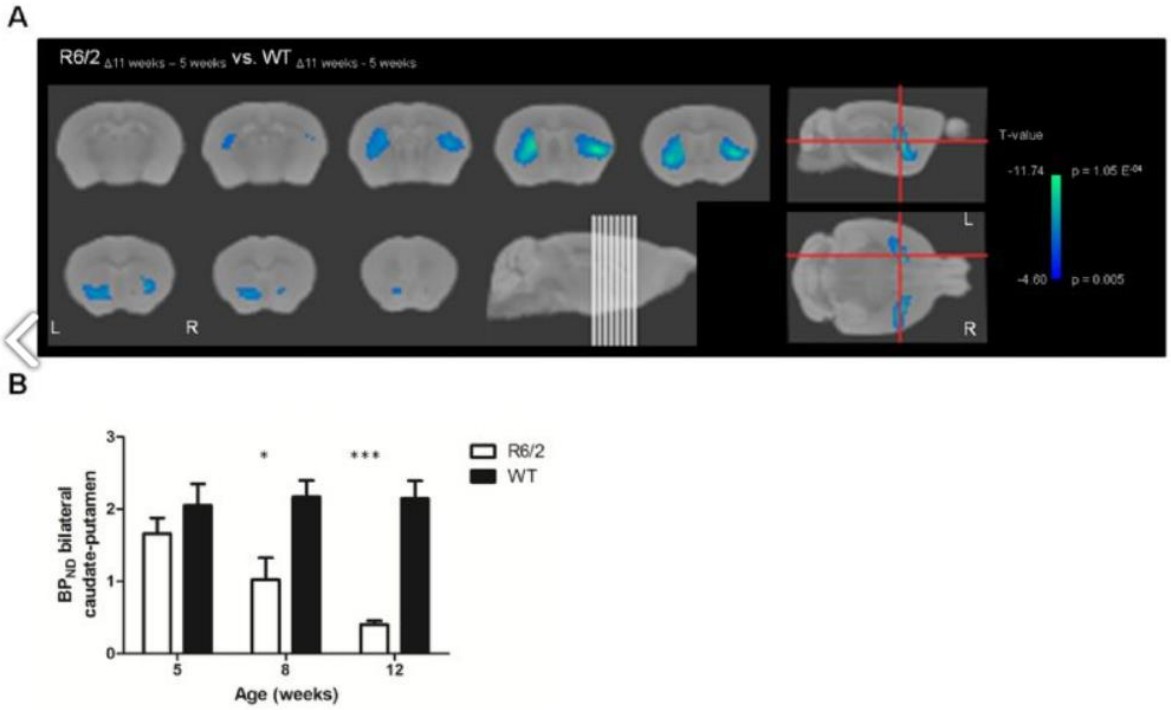

Fig2: PDE10A in R6/2: (A) Coronal brain sections showing decreased PDE10A binding potential in R6/2 mice over time, as compared to WT littermates. (B) Histograms of BP values of the bilateral caudate-putamen in R6/2 and WT animals over time. 2-way ANOVA; *p<0.05; ***p<0.001

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R6/2:
(A-B) Coronal and axial brain sections showing decreased

R6/2:
(A) Coronal brain sections showing decreased PDE10A